Synthesis and Antimicrobial Activity of New Tetrahydro-Naphthalene-Thiazolidinedione and Thiohydantoine Derivatives

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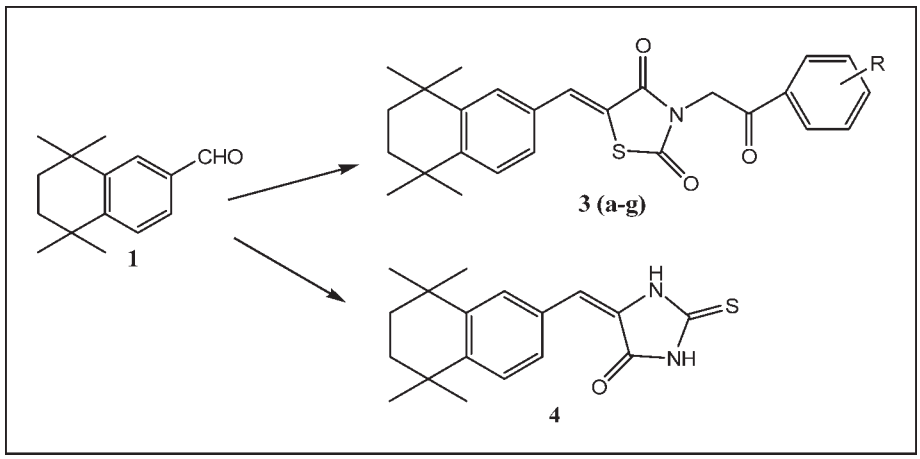

As part of an ongoing program aimed at recognizing novel antioxidant, antimicrobial, and anticancer molecules, herein we report the synthesis and biological evaluation of imidazolidin-4-one and thiazolidine-2,4-dione derivatives as antimicrobial agents. These compounds were prepared from 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-carboxaldehyde and 3-substituted phenacyl-2,4-thiazolidinediones using Knoevenagel reaction. The structures of compounds were confirmed by ^{1}H NMR, mass spectral data, and elemental analyses. The molecules were evaluated for *in vitro* antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (standard), methicillin-resistant *Staphylococcus aureus* (isolated), *Staphylococcus aureus* (SA), *Escherichia coli* (EC), *Bacillus subtilis* (BS), and *Candida albicans* (CA). Compounds **3**(**a–g**) and compound **4** showed equal and/or greater antimicrobial activity against MRSA and EC than ampicillin and sultamicillin.

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INTRODUCTION

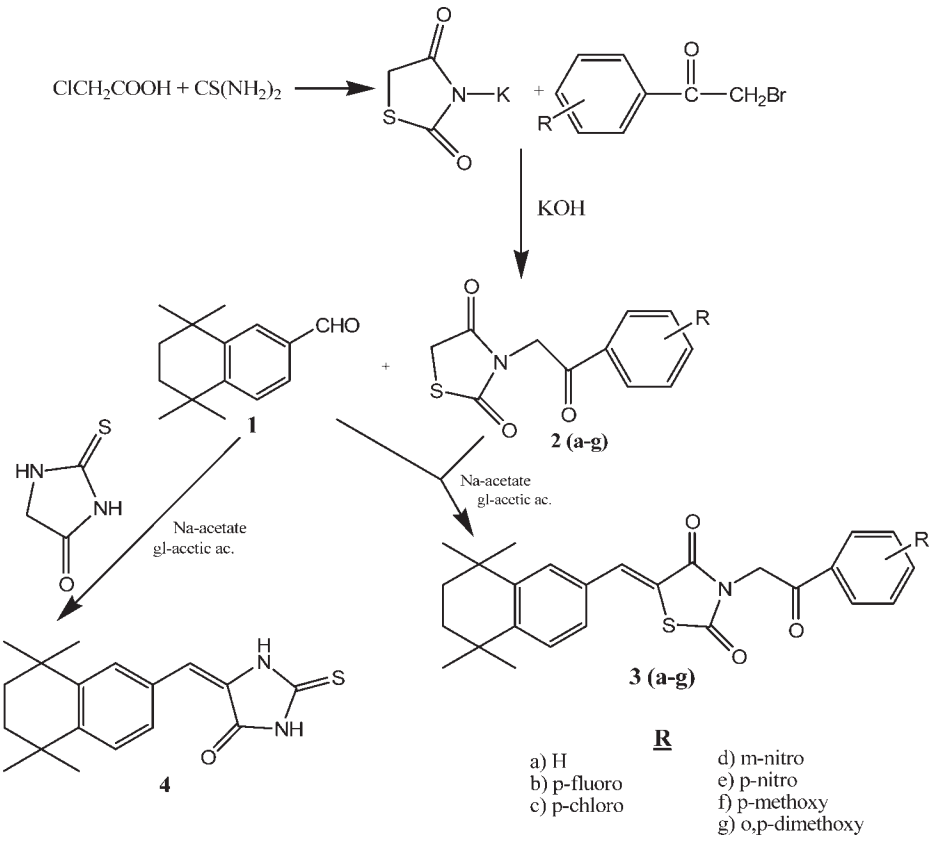
Previously, we reported that the synthesis and antimicrobial evaluation of tetrahydro-tetramethyl-naphthalene benzimidazoles, and tetrahydro-tetramethyl-naphthalene benzimidazole-amidines showed an activity comparable with that of fluconazole and sultamicillin against methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Candida krusei*, and *Candida albicans* [1,2].

Recent investigations have used retinoids both in chemotherapeutic and chemopreventive modes either as single agents or in combination with other agents such as growth factors and biological response modifiers [3]. The presence of a thiazolidine ring in penicillins and related derivatives was the first recognition of its occurence in nature [4]. The thiazolidinone nucleus is present in many compounds that have antibacterial and antifungal activity [5–9] This started the detailed structure-activity studies on thiazoline-2,4-diones and analogues related to them [10].

To provide more effective therapeutic agents with the benefical effects of all *trans*-retinoic acid (ATRA) but with reduced side effects, we developed conformationally constrained retinoids consisting of tetrahydro-tetramethyl-naphthalene moiety, which is integrated with thiazolidinedion and hydantoin ring systems and studied on their biological activity in terms of antimicrobial prospect.

In this article, synthesis and antimicrobial activity of a new series of 3-[2-(2,3,4-substitue-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione and 1-substitue-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-

Scheme 1. General synthesis of **3**(**a-g**) and **4**.



naphthalen-2-yl)-meth-(*E*)-ylidene]-2-thioxo-imidazolidine-4-one are described.

RESULTS AND DISCUSSION

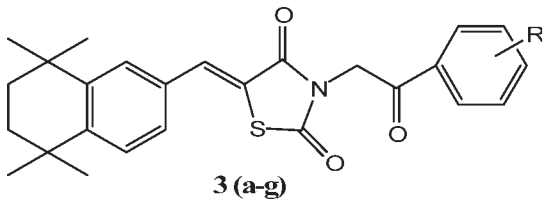
The synthetic procedure of the retinoidal thiazolidinedione derivatives is shown in Scheme 1. Because of the labile hydrogen atom at the 3-position, the thiazolidine-2,4-dione was *N*-alkylated with appropriate phenacyl halides in alkaline medium. The condensation of *N*-phenacylintermediates **2**(**a–g**) with retinoidal carboxaldehyde in glacial acetic acid and in the presence of sodium acetate by Knoevenagel reaction, led to 3-[2-(2,3,4-substitue-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione derivatives **3**(**a–g**).

The appearance of pathogens resistant to known antibiotic therapy is becoming an important healthcare problem including the increase in the isolation and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) strains [11]. Besides resistance to beta-lactam antibiotics, MRSA strains are also found to possess resistance to several antibiotics (macrolides, tetracyclines, and aminoglycosides) other than beta-lactams. Although MRSA are resistant to many drugs, most remain susceptible to the antibiotics vancomycin, teicoplanin (belongs to a group of antibiotics called glycopeptides), and linezolid [12,13]. Linezolid is a new antibiotic that is found active against MRSA and has good safety, tolerability even for newborns and children [14]. The chemical structure of linezolid is related to oxazolidine moiety, which is quite similar to those we have synthesized thiazolidinedione retinoids. The oxazolidinones, including linezolid and eperezolid, denote a unique class of synthetic antimicrobial agents with good activity against MRSA and vancomycin-resistant enterococci. Because of their unique mode of action, they do not display cross-resistance with other classes of antimicrobial agents [15].

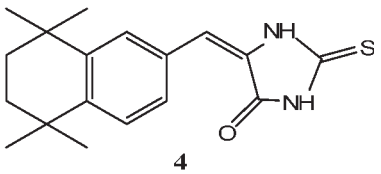
In our study, the prepared compounds [novel compounds **3**(**a–g**) and **4**] were screened *in vitro* against *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (standard) (ATCC 43300), methicillin-resistant *Staphylococcus aureus* (isolated), *Escherichia coli* (ATCC 23556), *Bacillus subtilis* (ATCC 6633), and *Candida albicans* (ATCC10145) by dilution method and ciprofloxacin, ampicilline, sultamicillin, and fluconazole were used as standard drugs whose minimum inhibitory concentration (MIC) values

Table 1

The structures and *in vitro* antimicrobial activities of compounds **3a–g** and **4**.



3 (a-g)



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Compounds	R	MRSA (Standard)	MRSA (Isolated)	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*
3a	H	25	25	50	50	25	25
3b	*p*-fluoro	50	50	50	50	25	12.5
3c	*p*-chloro	50	50	50	50	50	6.25
3d	*m*-nitro	25	25	50	50	25	12.5
3e	*p*-nitro	25	25	50	25	50	6.25
3f	*p*-methoxy	25	25	25	25	50	25
3g	*o*,*p*-dimethoxy	50	50	50	25	50	3.125
4		50	50	50	25	3.125	6.25
Cipro		6.25	12.5	0.78	0.19		
Ampicillin		50	50	0.78	50	50	
Sultamicilin		50	50	1.56	25	0.78	
Fluconazole							1.56

MIC, minimum inhibitory concentration μg/mL.

are provided (Table 1). The results of the antimicrobial screening showed that the thiazolidinedione derivatives integrated to partial retinoic acid moiety exhibited varying degrees of moderate activity against bacteria comparable with ampicilline and sultamiclline on MRSA. Moreover, compounds **3c**, **3e**, **3g**, and **4** were active toward *C. albicans*. The MICs ranging between 3.125 and 25 μg/mL were reported for these compounds.

EXPERIMENTAL

Chemistry. Melting points were determined with a Buchi SMP-20 and Buchi 9100 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer in DMSO-d_6, chemical shifts are expressed as δ (ppm) values with tetramethylsilane (TMS) as an internal standard and coupling constants (*J*) are reported in Hertz (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). The mass spectra were recorded with a Waters ZQ micromass LC-MS spectrometer by the method of ES$^+$ and elemental analyses were performed on LECO 932 CHNS instrument and were within ±0.5% of the theoretical values (analyses performed at Scientific and Technical Research Council of Turkey, Instrumental Analysis Center, Ankara, Turkey). Analytical thin-layer chromatography (TLC) was run on Merck silica gel plates (Kieselgel 60F-254). Column chromatographies were accomplished on silica gel 60 (40-63 μm particle size) (Merck). All starting materials and reagents were high-grade commercial products purchased from Aldrich, Merck or Fluka. Compound **2a**, **2c**, **2e** [16], **2b** [17], **2d** [18], **2f–g** [19], and retinoidal-carboxaldehyde **1** [20] were prepared according to the literature.

General synthesis of compounds 3a-g and 4. 3-(Substituted phenacyl)-2,4-thiazolidinedione 2a–g or thiohydantoine (1 mmol) and CH_3COONa (0.25 g) were added to a solution of retinoidal carboxaldehyde 1 (1.2 mmol) in glacial CH_3COOH (3 mL). The reaction mixture was heated to 140–150°C for a period of 4-6 h. The resulting precipitate was filtered, washed with H_2O, and then with acetone. The residue was purified by column chromatography silica gel 60 (230–400 mesh ASTM) using *n*-hexane: $CHCl_3$ (2:1) mL or *n*-hexane: EtOAc (3:1) mL as eluant [18].

3-[2-(Phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3a). Yield: 42%, mp: 197°C, ^{1}H NMR (DMSO): 1.5 (d,12 H, *J* = 9.2), 1.65 (s, 4H), 5.34 (s, 2 H, CH_2), 7.4 (dd, 1H, *J* = 6.8, *J* = 1.6), 7.52 (d, 1H, *J* = 8), 7.6 (t, 1H), 7.65 (d, 1H, *J* = 1.6), 7.74 (t, 1H), 7.98 (s, 1H, =CH) 8.09 (d, 2H, *J* = 6.8). MS (ESI+) *m/z*: 434 (M+1, 100) Anal. for $C_{26}H_{27}NO_3S$ Calcd. C: 72.03 H: 6.28 N: 3.23 S: 7.40 found C: 71.87 H: 6.24 N: 3.26 S: 7.39.

3-[2-(4-Flouro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3b). Yield: 44%, mp: 199°C, ^{1}H NMR (DMSO): 1.3 (d, 12 H, *J* = 9.2), 1.67 (s, 4H), 5.35 (s, 2 H, CH_2), 7.39–7.56 (m, 4H), 7.67 (d, 1H, *J* = 1.6), 7.99 (s, 1H, =CH), 8.19 (m, 2H). MS (ESI+) *m/z*: 452 (M+1, 100) Anal. for $C_{26}H_{26}FNO_3S.0.2\ H_2O$ Calcd. C: 68.60 H: 5.84 N: 3.07 S: 7.05 found C: 68.39 H: 5.68 N: 3.10 S: 6.98.

3-[2-(4-Chloro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3c). Yield: 45%, mp: 195°C, ^{1}H NMR (DMSO): 1.3 (d, 12 H, *J* = 8.8), 1.65 (s, 4H), 5.35 (s, 2 H,

CH_2), 7.42 (dd, 1H, J = 6.8, J = 2), 7.54 (d, 1H, J = 8.8), 7.68 (m, 3H), 7.99 (s, 1H, =CH) 8.12 (d, 2H, J = 8.4). MS (ESI+) *m/z*: 468 (M+1, 75) Anal. for $C_{26}H_{26}ClNO_3S.0.1$ $CHCl_3 0.2$ H_2O Calcd. C: 64.90 H: 5.53 N: 2.90 S: 6.62 found C: 64.80 H: 5.08 N: 2.90 S: 6.12.

3-[2-(3-Nitro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3d). Yield: 38%, mp: 139°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 9.2), 1.67 (s, 4H), 5.48 (s, 2 H, CH_2), 7.42 (dd, 1H, J = 6.8, J = 1.6), 7.54 (d, 1H, J = 8.4), 7.67 (d, 1H, J = 1.2), 7.92 (t, 1H), 8.01 (s, 1H, =CH) 8.57 (m, 2H), 8.78 (s, 1H). MS (ESI+) *m/z*: 479 (M+1, 100) Anal. for $C_{26}H_{26}N_2O_5S.0.1$ C_6H_6 Calcd. C: 65.69 H: 5.51 N: 5.75 S: 6.59 found C: 66.05 H: 5.14 N: 5.75 S: 6.23.

3-[2-(4-Nitro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3e). Yield: 42%, mp: 181°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 9.2), 1.67 (s, 4H), 5.35 (s, 2 H, CH_2), 7.42 (d,1H, J = 8.4), 7.54 (d, 1H, J = 8.4), 7.67 (s, 1H), 8.01 (s, 1H, =CH), 8.31–8.44 (m, 4H). MS (ESI+) *m/z*: 479 (M+1, 100) Anal. for $C_{26}H_{26}N_2O_5S.0.1$ C_6H_6 Calcd. C: 65.25 H: 5.48 N: 5.85 S: 6.70 found C: 65.31 H: 5.44 N: 5.83 S: 6.61.

3-[2-(4-Dimethoxy-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3f). Yield: 47%, mp: 146°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 8.8), 1,67 (s, 4H), 3,88 (s, 3H), 5.26 (s, 2 H, CH_2), 7.12 (d, 2H, J = 8.8), 7.41 (dd, 1H, J = 6.4, J = 2), 7.53 (d, 1H, J = 8.4), 7.66 (d, 1H, J = 2), 7.99 (s, 1H, =CH) 8.07 (d, 2H, J = 8.8). MS (ESI+) *m/z*: 464 (M+1, 100) Anal. for $C_{27}H_{29}NO_4S$ Calcd. C: 69.95 H: 6.31 N: 3.02 S: 6.92 found C: 69.79 H: 6.25 N: 3.09 S: 6.90.

3-[2-(2,5-Dimethoxy-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3g). Yield: 43%, mp: 151°C, ^{1}H NMR (DMSO): 1.46 (d, 12 H, J = 9.2), 1,53 (s, 4H), 3,55 (s, 3H), 3,59 (s, 3H),5.1 (s, 2 H, CH_2), 7.27 (m, 3H), 7.42 (d, 1H, J = 8.4), 7.54 (d, 1H, J = 8.4), 7.66 (d, 1H, J = 1.6), 7.98 (s, 1H, =CH). ^{13}C NMR (DMSO) δ 191.46, 167.80, 165.97, 154.84, 153.80, 148.71, 146.31, 134.85, 130.93, 129.95, 128.34, 127.58, 124.35, 122.96, 120.28, 115.18, 113.98, 57.18, 56.29, 52.16, 34.97, 34.94, 34.70, 32.15, 31.92. MS (ESI+) *m/z*: 494 (M+1, 50) Anal. for $C_{28}H_{31}NO_5S$ Calcd. C: 68.13 H: 6.33 N: 2.84 S: 6.50 found C: 67.80 H: 5.89 N: 2.85 S: 6.37.

5-[1-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methl-(E/Z)-ylidene]-2-thioxo-imidazolidine-4-one (4). Yield: 32%, mp: 207°C, ^{1}H NMR (DMSO): 1.26 (d, 12 H, J = 13.2), 1,64 (s, 4H), 6.47 (s, 1H, =CH), 7.37–7.6 (m, 3H, Ar—H), 12.14 (s, 1H), 12.36 (s, 1H). MS (ESI+) *m/z*: 315 (M+1, 100) Anal. for $C_{18}H_{21}N_2OS.0.1$ $CHCl_3$ Calcd. C: 66.84 H: 6.54 N: 8.61 S: 9.83 found C: 66.77 H: 6.56 N: 8.46 S: 9.51. According to the literatures, the thiazolidinedione compounds usually possess the *Z* configuration [21–23]. On the other hand, 5-arylidene-4-thio-imidazolidine-2-ones are theoretically able to exist both in the *Z* and *E* configurations. To explain configurations of our thio-imidazolidine compound. The NOESY and ROESY spectra of the compound 4 showed the compound is a mixture of *E* (more in amount) and *Z* configurations.

Microbiology. Determination of the minimal inhibitory concentrations (MIC) of the compounds by dilution method.

Sample preparation. Each of the test compounds and standards (ampicillin, floconazole, cipro, and sultamicilin) were dissolved in 12.5% DMSO, at concentrations of 200 μg/mL. Further dilutions of the compounds and standards in the test medium were prepared at the required quantities of 100, 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 μg/mL.

Culture of microorganims. All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and the yeasts *Candida albicans*. The bacterial strains and *Candida albicans* used in this study were obtained from the culture collection of Refik Saydam Health Institution of Health Ministry, Ankara, and maintained at the Microbiology Department of Faculty of Pharmacy of Ankara University. The bacterial strains were maintained on MHA (Mueller-Hinton Agar) medium for 24 h at 37°C and fungi were maintained on SDA (Sabouraud Dextrose Agar) for 2–5 days at 25°C ± 1°C. The bacteria and fungi inocula were prepared by suspension in 9 mL of sterile water for colonies from culture on MHA and SDA medium.

Assay for in vitro antimicrobial activity. The *in vitro* antimicrobial activity of compounds was tested by the tube dilution technique [24,25]. The tube dilution technique was followed to determine the MIC of all the synthesized compounds. MHB (Mueller-Hinton Broth) was used for bacteria, and SDB (Sabouraud Dextrose Broth) was used for *Candida spp*. The cell density of each inoculum was adjusted in sterile water of a 0.5 Mc Farland standard. A final concentration of $\sim 10^5$ CFU/mL and 10^4 CFU/ mL for the bacteria and fungi, respectively. Microbial inocula were added to the twofold diluted samples. After incubation for bacteria 18–24 h at 37°C ± 1°C and for fungi 2–5 days 25°C ± 1°C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μg/mL.

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REFERENCES AND NOTES

[1] Ates-Alagoz, Z.; Alp, M.; Kus, C.; Yildiz, S.; Buyukbingol, E.; Goker H. Arch Pharm Chem Life Sci 2006, 339, 74.

[2] Ates-Alagoz, Z.; Yildiz, S.; Buyukbingol, E. Chemotherapy 2007, 53, 110.

[3] Eyrolles, L.; Kagechika, H.; Kawachi, E.; Fukasawa, H.; Iijima, T.; Matsushima, Y.; Hashimoto, Y.; Shudo, K. J Med Chem 1994, 37, 1508.

[4] Brown, F. C. Chem Rev 1961, 61, 463.

[5] Nasr, M. N.; Gineinah, M. M.; El-Bendary, E. R. Arch Pharm 2003, 336, 560.

[6] Tuncbilek, M.; Altanlar, N., II. Farmaco 1999, 54, 475.

[7] Labouta, I. M.; Salama, H. M.; Ashba, N. H.; Kader, O.; El-Chrbini, E. Eur J Med Chem 1987, 22, 485.

[8] Goes, A. J. S.; DeLima, M. C. A.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C. Ann Pharm Françaises 1991, 49, 92.

[9] Lima, M. C. A.; Costa, D. L. B.; Goes, A. J. S.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C. Pharmazie 1992, 47, 182.

[10] Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. Chem Rev 1981, 81, 175.

[11] Chu, D. T. W.; Plattner, J. J.; Katz, L. New directions in antibacterial research. J Med Chem 1996, 39, 3853.

[12] Gonzales, C.; Rubio, M.; Romero-Vivas, J.; Gonzales, M.; Picazzo, J. J. Clin Infect Dis 1999, 29, 1171.

[13] Jones, K.; Cooper, B.; Singer, M.; Wilson, A. P. R.; Kibbler, C.; Cepeda, J. A.; Whitehouse, T.; Hails, J.; Kwaku, F.; Taylor, L.; Hayman, S.; Shaw, S.; Shulman, R. J Antimicrob Chemother 2004, 53, 345.

[14] Marchese, A.; Schito, G. C. Clin Microbiol Infect 2001, 7 (Suppl 4), 66.

[15] Rybak, M. J.; Cappelletty, D. M.; Moldovan, T.; Aeschlimann, J. R.; Kaatz, G. W. Antimicrob Agents Chemother 1998, 42, 721.

[16] Salama, H. M.; Labouta, I. M.; Moustafa, M. A. Alex J Pharm Sci 1990, 4, 44–46.

[17] de Lima, J. G.; Perrissin, M.; Chantegrel, J.; Luu-Duc, C.; Rousseau, A.; Narcisse, G. Arzneim-Fors/Drug Res 1994, 44, 831.

[18] Tuncbilek, M.; Altanlar, N. Arch Pharm Chem Life Sci 2006, 339, 213.

[19] Ayhan-Kilcigil, G.; Altanlar, N. Arzneim-Fors/Drug Res 2000, 50, 154.

[20] Ates-Alagoz, Z.; Buyukbingol, E. Heterocyclic Commun 2001, 7, 455.

[21] Tan, S.-F.; Ang, K.-P.; Fong, Y.-F. J Chem Soc Perkin Trans II 1986, 1941.

[22] Vögeli, U.; Philipsborn, W.; Nagarajan, K.; Nair, M. D. Helv Chim Acta 1978, 61, 607.

[23] Albuquerque, J. F.; Albuquerque, A.; Azevedo, C. C.; Thomasson, F.; Galdino, L. C.; Chantegrel, J.; Catanho, M. T.; Pitta, I. R.; Luu-Duc, C. Pharmazie 1995, 50, 387.

[24] National Committee on Clinical Laboratory Standards (NCCLS). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, Approved Standard M27-A. NCCLS: Wayne, PA; 1997, Vol. 17, p 9.

[25] National Committee on Clinical Laboratory Standards (NCCLS). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard M7-A5. NCCLS: Wayne, PA; 2000, Vol. 20, p 2.